Anesthesiology
V 38, No 2, Feb 1973

# Laboratory Note

## *The Lack of Effect of Lidocaine on Oxyhemoglobin Dissociation*

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SEVERAL INVESTIGATORS have studied the effects of inhalation anesthetics on the oxyhemoglobin-dissociation curve. Diethyl ether, Ethrane, nitrous oxide, and cyclopropane have been shown to shift the curve to the right *in vivo*.[1] An increase in $P_{50}$ (oxygen tension at which hemoglobin is 50 per cent saturated) of 0.5 to 7 torr has been shown for halothane using dog blood *in vivo* and human blood *in vitro*.[2,3] Recent studies by Weiskopf *et al.*[4] revealed a direct effect of halothane on the oxygen polarographic electrode, accounting for the change in $P_{50}$ detected by previous studies.

The present study was designed to investigate the effect of a local anesthetic on the oxyhemoglobin-dissociation curve.

### Methods

Venous blood was drawn from each of 16 nonsmoking hospital patients scheduled for minor surgical procedures. The blood was collected into a sterile 50-ml glass syringe whose deadspace had been filled with heparin and studied immediately. The syringe was kept in ice between determinations. A first blood sample was drawn from each patient on the afternoon prior to the day of surgery and a second sample early in the morning of the operative day before premedication was given. Nothing was added to the first sample, which served as a control. Lidocaine HCl (ASTRA Pharmaceutical Products, Inc., 0.5 per cent, 50-ml multiple-dose vial) was added to the second sample to achieve a concentration of 7.3 μg/ml plasma, a level slightly higher than those at which symptoms of toxicity first appear.[5] The effect of obtaining the control sample the afternoon before and the lidocaine sample early in the morning was considered not significant.

TABLE 1. Mean Corrected Blood–Gas Values

| | Control | Lidocaine |
|---|---|---|
| 4.0 per cent oxygen | | |
| $P_{O_2}$ | 28.39* | 27.95 |
| SD | 1.48 | 0.96 |
| $P_{CO_2}$ | 41.65 | 41.66 |
| SD | 0.67 | 0.66 |
| *p*H | 7.40 | 7.39 |
| SD | 0.03 | 0.03 |
| 5.8 per cent oxygen | | |
| $P_{O_2}$ | 41.15 | 40.77 |
| SD | 2.23 | 2.03 |
| $P_{CO_2}$ | 39.85 | 39.93 |
| SD | 0.63 | 0.62 |
| *p*H | 7.40 | 7.39 |
| SD | 0.02 | 0.02 |

* Mean value for 16 samples.

Both control and lidocaine-treated samples were equilibrated in a modified Farhi tonometer[6] with four gases of known concentrations of oxygen, carbon dioxide, and nitrogen. Oxygen percentages were 0, 4.0, 5.8, and 45.0. All mixtures had approximately 6 per cent carbon dioxide, and the balance was nitrogen.

A 6-ml sample was tonometered 20–30 minutes in a sterile tonometer flask. Following equilibration, a 4-ml portion was withdrawn anaerobically and used for simultaneous measurement of hemoglobin saturation and blood gases. Two additional 6-ml samples were tonometered a similar length of time using the 4.0 and 5.8 per cent oxygen mixtures, and again simultaneous measurements of $P_{O_2}$ and hemoglobin saturation were made. Hemoglobin saturation was determined spectrophoto-

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Received from the Anesthesia and Operative Service, Brooke General Hospital, Brooks Army Medical Center, Fort Sam Houston, Texas 78234. Accepted for publication August 11, 1972.

TABLE 2. Per Cent Saturation and Corresponding Corrected Oxygen Tensions

| | Oxygen (Per Cent) | Control | | Lidocaine | |
|---|---|---|---|---|---|
| | | $Pao_2$ (torr) | Per Cent Saturation | $Pao_2$ (torr) | Per Cent Saturation |
| Subject 1 | 4.0 | 27.99* | 58.8 | 25.93 | 49.01 |
| | 4.0 | 28.43* | 59.7 | 26.31 | 54.35 |
| | 5.8 | 42.33 | 88.0 | 38.13 | 77.36 |
| | 5.8 | 40.25 | 84.3 | 39.94 | 73.39 |
| Subject 2 | 4.0 | 25.23 | 50.6 | 27.37 | 43.8 |
| | 4.0 | 28.0 | 61.2 | 26.57 | 46.7 |
| | 5.8 | 38.45 | 78.0 | 41.11 | 79.6 |
| | 5.8 | 38.88 | 78.9 | 38.0 | 79.3 |
| Subject 3 | 4.0 | 28.4 | 55.5 | 27.62 | 46.4 |
| | 4.0 | 28.75 | 55.6 | 29.74 | 49.9 |
| | 5.8 | 40.34 | 76.0 | 39.57 | 73.8 |
| | 5.8 | 39.17 | 78.3 | 41.61 | 78.3 |
| Subject 4 | 4.0 | 29.83 | 54.1 | 28.92 | 54.0 |
| | 4.0 | 28.71 | 56.4 | 29.15 | 59.3 |
| | 5.8 | 42.73 | 79.7 | 43.33 | 76.9 |
| | 5.8 | 42.87 | 80.0 | 40.84 | 80.3 |
| Subject 5 | 4.0 | 26.89 | 54.6 | 28.42 | 61.46 |
| | 4.0 | 29.34 | 56.0 | 30.21 | 61.04 |
| | 5.8 | 39.57 | 80.9 | 42.63 | 83.98 |
| | 5.8 | 37.27 | 81.3 | 41.76 | 84.80 |
| Subject 6 | 4.0 | 28.34 | 58.43 | 28.61 | 55.72 |
| | 4.0 | — | — | 27.65 | 56.42 |
| | 5.8 | 37.32 | 88.47 | 40.66 | 78.65 |
| | 5.8 | 49.46 | 94.10 | 39.73 | 80.50 |
| Subject 7 | 4.0 | 28.09 | 61.01 | 27.95 | 53.99 |
| | 4.0 | 28.33 | 63.74 | 28.51 | 58.62 |
| | 5.8 | 42.27 | 82.67 | 39.70 | 75.90 |
| | 5.8 | 40.49 | 85.95 | 38.87 | 78.11 |
| Subject 8 | 4.0 | 28.8 | 54.24 | 28.19 | 44.34 |
| | 4.0 | 29.23 | 53.54 | 27.61 | 44.57 |
| | 5.8 | 40.62 | 78.45 | 39.80 | 68.52 |
| | 5.8 | 40.50 | 79.49 | 39.66 | 74.38 |
| Subject 9 | 4.0 | 28.69 | 54.27 | 27.50 | 50.29 |
| | 4.0 | 29.06 | 60.20 | 27.22 | 55.76 |
| | 5.8 | 41.83 | 79.47 | 39.46 | 78.59 |
| | 5.8 | 41.35 | 83.44 | 39.50 | 79.57 |
| Subject 10 | 4.0 | 29.10 | 57.22 | 26.76 | 58.06 |
| | 4.0 | 29.82 | 61.46 | 26.96 | 64.09 |
| | 5.8 | 41.74 | 83.13 | 38.82 | 79.59 |
| | 5.8 | 41.09 | 82.72 | 39.98 | 83.86 |
| Subject 11 | 4.0 | 29.92 | 55.72 | 27.90 | 56.74 |
| | 4.0 | 29.53 | 59.76 | 27.49 | 60.92 |
| | 5.8 | 42.87 | 78.37 | 40.53 | 78.44 |
| | 5.8 | 41.97 | 80.53 | 42.38 | 81.97 |

TABLE 2. *(Continued)*

| | Oxygen (Per Cent) | Control | | Lidocaine | |
|---|---|---|---|---|---|
| | | $P_{aO_2}$ (torr) | Per Cent Saturation | $P_{aO_2}$ (torr) | Per Cent Saturation |
| Subject 12 | 4.0 | 27.73 | 54.78 | 28.12 | 57.55 |
| | 4.0 | 28.28 | 59.44 | 28.19 | 56.44 |
| | 5.8 | 41.85 | 78.01 | 49.34 | 84.56 |
| | 5.8 | 39.93 | 79.06 | 39.92 | 79.35 |
| Subject 13 | 4.0 | 29.78 | 49.91 | 27.47 | 53.13 |
| | 4.0 | 25.38 | 49.69 | 27.46 | 49.62 |
| | 5.8 | — | — | 41.22 | 78.80 |
| | 5.8 | 39.68 | 75.77 | 39.99 | 76.41 |
| Subject 14 | 4.0 | 27.77 | 55.50 | 28.18 | 59.39 |
| | 4.0 | 31.97 | 57.75 | 27.92 | 62.29 |
| | 5.8 | 42.83 | 79.69 | 42.19 | 78.38 |
| | 5.8 | 43.38 | 81.94 | 40.79 | 81.05 |
| Subject 15 | 4.0 | 27.25 | 52.68 | 28.86 | 57.09 |
| | 4.0 | 27.09 | 51.54 | 28.63 | 58.73 |
| | 5.8 | 41.28 | 75.83 | 41.92 | 79.24 |
| | 5.8 | 39.32 | 78.10 | 41.13 | 85.53 |
| Subject 16 | 4.0 | 29.05 | 56.35 | 29.17 | 56.50 |
| | 4.0 | 29.43 | 62.51 | — | — |
| | 5.8 | 41.76 | 81.78 | 41.99 | 81.66 |
| | 5.8 | 42.10 | 84.81 | 40.02 | 79.48 |

* Not duplicates. Repeat samples were equilibrated separately.

metrically using the Beckman DU Spectrophotometer as described by Nahas [7] after hemolysis with Triton X100.[8] Blood gases were measured using Instrumentation Laboratories microelectrodes immersed in the tonometer constant-temperature bath. Temperature was kept at a constant 37 C, according to a N.B.S. thermometer. The electrodes were calibrated prior to each determination and sloped at least twice daily using calibrating-gas tensions based on daily mercurial barometric pressure readings corrected for temperature and gravity. Hematocrits were measured initially and after each determination. A sample of each subject's blood was analyzed electrophoretically for hemoglobin type. Erythrocyte 2,3-diphosphoglycerate (2,3-DPG) concentrations [9] of all control and lidocaine-treated samples were measured before and after 90-minute storage in ice, using an enzymatic ultraviolet method and reagents supplied by Sigma Chemical Company.

Each measured oxygen tension was corrected for the calculated gas/blood ratio of our electrode ($1.02 \times$ observed $P_{O_2}$ = corrected $P_{O_2}$). Further correction of $P_{O_2}$ was done to standardize to *p*H 7.4, using the formula [10]:

$$\Delta \log P_{O_2} = -0.48\ \Delta pH + 0.0013\ \Delta\ BE$$

Base excess was determined from the Siggaard-Andersen nomogram.[11]

The two determinations for each patient were averaged prior to statistical analysis. A three-factor analysis of variance procedure was used to analyze per cent hemoglobin saturation data. Factors analyzed were: 1) subjects; 2) treatment (control *vs.* lidocaine); 3) oxygen percentage.

## Results

The corrected mean blood–gas values and standard deviations, arranged according to equilibration oxygen percentages, are given in table 1. Corrected $P_{O_2}$ and their correspond-

ing oxyhemoglobin-saturation percentages for each patient are listed in table 2. The mean for lidocaine-treated samples was less than the control mean at each oxygen level, but the difference between the means was not significant. Hematocrit and 2,3-DPG values were all normal and did not change during the determinations. All patients had normal adult hemoglobin.

## Discussion and Conclusions

The significant difference between our first and second $P_{O_2}$ and hemoglobin saturation values warrants clarification. The repeat values for each oxygen percentage represent blood samples equilibrated separately in different tonometer flasks, not duplicate values for blood from the same flask. Where a repeat oxygen tension differs from the initial value, there is a corresponding lower or higher hemoglobin saturation value. Had the two sets of values been true duplicates, the variation might cast doubt upon the accuracy of the Nahas method. The spectrophotometric method of measuring hemoglobin saturation, however, has been shown to be as accurate as the Van Slyke manometric method [12] provided hemoglobin values are between 10 and 20 g/100 ml.

Local anesthetics may alter hemoglobin erythrocyte function. The structural configuration of hemoglobin is altered by oxygenation.[13] A possible analogous change occurs when cyclopropane binds to myoglobin, altering its tertiary structure.[14] Halothane has been shown to bind to the beta chain of hemoglobin.[15] Studies indicate that local anesthetics are capable of reacting through electrostatic forces with membrane phospholipids, to prevent cation binding and stabilization of the cellular membrane to sodium and potassium flux.[16] Hydrogen bonding at the cell membrane and interaction with proteins have been proposed as a mechanism of action of local anesthetics.[17, 18] There is also evidence that these drugs upset oxidative phosphorylation and tissue respiration.[19] The postulate that lidocaine can bind with hemoglobin or erythrocyte membrane phospholipids or alter erythrocyte membrane mechanics was not investigated. Experimental conditions were carefully controlled to eliminate the multitude of cofactors affecting the oxyhemoglobin-saturation curve.

The clinically toxic dose of lidocaine does not significantly alter the oxyhemoglobin-saturation curve *in vitro*.

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